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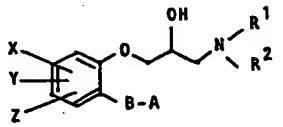
(54) Benzylazole derivatives.

(57) The invention relates to benzylazole derivatives of the general formula I



(1)

wherein A, B, R^1, R^2, X, Y and Z have the meanings indicated in the patent claim. The compounds are useful as anti-arrhythmic agents and are obtained by reacting the corresponding 2,3-epoxypropyloxybenzylazole with a primary or secondary amine.

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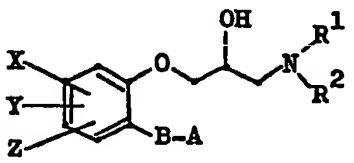
Case: F 4371 MY
Shionogi & Co., Ltd., Osaka, Japan May 13, 1982

"BENZYLAZOLE DERIVATIVES"

The present invention relates to benzylazole derivatives useful as antiarrhythmics.

The benzylazole derivatives are represented by the formula:



(I)

(wherein

A is a 5- or 6-membered unsaturated heterocycle containing 1-3 nitrogen atoms or a benzimidazolyl optionally each substituted by 1-3 substituents selected from oxo, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_2-C_6 alkoxycarbonyl and halogen;

B is $>CHR^3$ or $>C=CR^4R^5$

in which R^3, R^4 and R^5 are independently hydrogen or C_1-C_4 alkyl;

R^1 is C_1-C_4 alkyl;

R^2 is hydrogen or C_1-C_4 alkyl; or

R^1-N-R^2 is pyrrolidinyl, piperidino, piperazino or morpholino; and

X, Y and Z are independently hydrogen, C_1-C_4 alkyl, C_1-C_4 alkoxy or halogen)

and pharmaceutically acceptable acid addition salts thereof are included in the present invention.

The terms used in the above definition are illustratively exemplified below:

C_1-C_4 alkyl includes methyl, ethyl, propyl, i-propyl, butyl, i-butyl, s-butyl, t-butyl;

C_1-C_4 alkoxy includes methoxy, ethoxy, propoxy, i-propoxy, butoxy, i-butoxy;

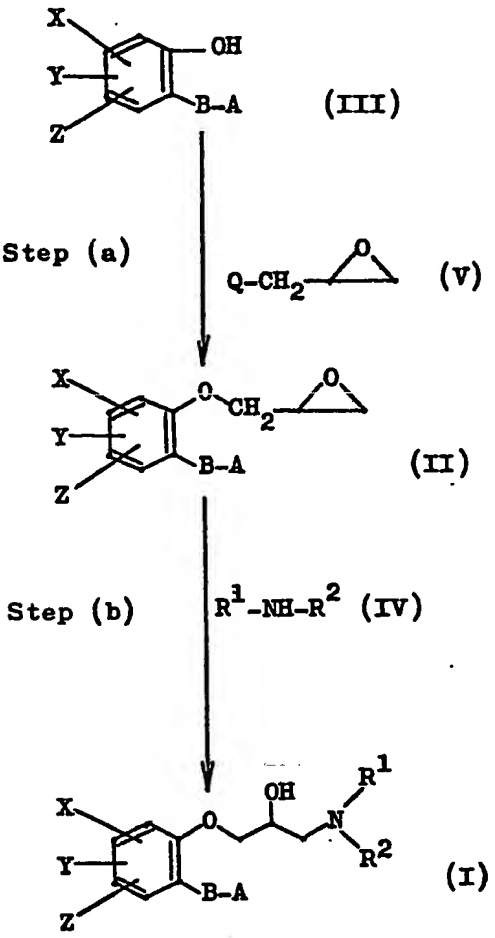
C_2-C_6 alkoxycarbonyl includes methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, pentyloxycarbonyl;

halogen includes fluorine, chlorine, bromine, iodine;

the 5- or 6-membered unsaturated heterocycle containing 1-3 nitrogen atoms includes pyrrole, imidazole, triazole, pyridine, pyridazine, pyrimidine, pyrazine, triazine, on which 1-3 substituents selected from oxo, C_1-C_4 alkyl, C_2-C_6 alkoxycarbonyl and halogen may optionally exist.

The pharmaceutically acceptable acid addition salts of Compounds I illustratively include salts with inorganic acids such as sulfuric acid, hydrochloric acid, hydrobromic acid or phosphoric acid and those with organic acids such as acetic acid, citric acid, maleic acid, malic acid, succinic acid, tartaric acid, cinnamic acid, benzoic acid, methanesulfonic acid or ascorbic acid.

The compounds of general formula I may be prepared in accordance with the following reacti n scheme:



(wherein A, B, R^1, R^2, X, Y and Z have the same significance as given earlier; and Q is halogen (e.g. chlorine, bromine, iodine) or a leaving group (e.g. tosyloxy)).

Accordingly, the compounds of formula I are prepared by reacting the phenol derivative(III) with an epihalohydrin or 2,3-epoxypropyl ester (V) and reacting the resulting epoxide (II) with a primary or secondary amine (IV). Above steps are explained

in detail b low:

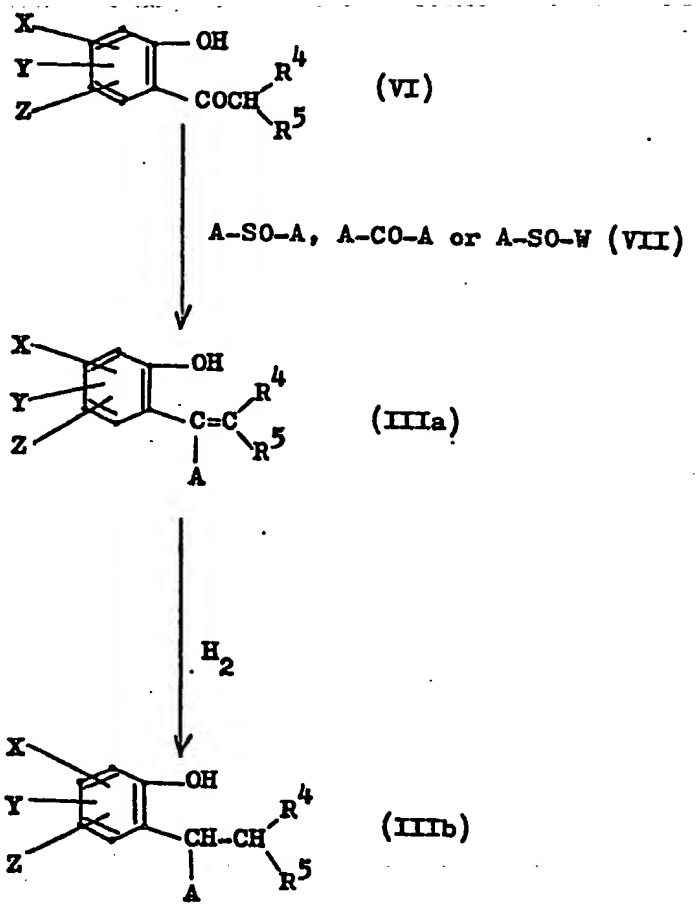
Step (a)

The phenol derivative (III) is reacted with an epihalohydrin (e.g. epibromohydrin, epichlorohydrin) or 1,2-epoxypropyl ester (e.g. 2,3-epoxypropyl tosylate)(V) in the presence of a base such as alkali hydroxide, alkali hydrogencarbonate, alkali carbonate, alkali alkoxide or alkali hydride in an appropriate solvent such as methanol, ethanol, benzene, toluene, dimethylformamide, dimethylsulfoxide at a temperature between room temperature and boiling point of the solvent used (e.g. 15 to 120°C).

Step (b)

The resulting epoxide (II) is reacted with a primary or secondary amine (IV) such as methylamine, ethylamine, i-propylamine, butylamine, i-butylamine, s-butylamine, t-butylamine, dimethylamine, methylethylamine, diethylamine, dipropylamine, di-i-propylamine, methylbutylamine, methyl-i-butylamine, or ethylbutylamine in the presence or absence of an appropriate solvent such as alcohols (e.g. methanol, ethanol), ethers (e.g. ether, tetrahydrofuran), or hydrocarbons (e.g. benzene, toluene, xylene) at between room temperature and boiling point of the solvent used (e.g. about 25 to about 100°C). In general, an excessive amount of the amine (IV) may play the part of the solvent.

The starting phenol (III) is prepared according to the following scheme:



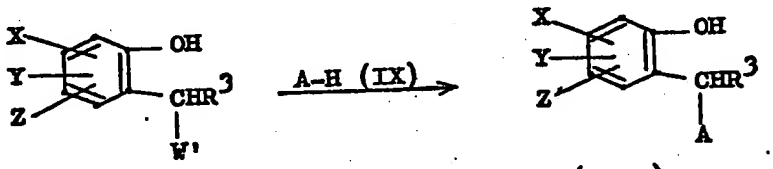
(wherein W is halogen (e.g. chlorine, bromine, iodine) and A, R^4, R^5, X, Y and Z have the same significance as given earlier)

At first Compound IIIa is prepared by reacting an acetophenone derivative (VI) with a thionyl or carbonyl compound (VII) in an appropriate solvent (e.g. methylene chloride, 1,2-dichloroethane, dimethylsulfoxide, acetonitrile, dimethylformamide) at room temperature or under cooling or heating, preferably at 10 to 60°C. For example,

2-[1-(1-imidaz lyl)vinyl]phenol is discl sed by Ogata et al. [Tetrahydron Letters, 52, 5011 (1979)] and 2-[1-(1-benzimidazolyl)vinyl]phenol is disclosed by Ogata et al. [Synthetic Communications, 10 (7), 559 (1980)].

Then Compound IIIb in which B is alkylene is prepared by hydrogenating Compound IIIa in a conventional manner.

Another starting compound (IIIc) is prepared as follows:



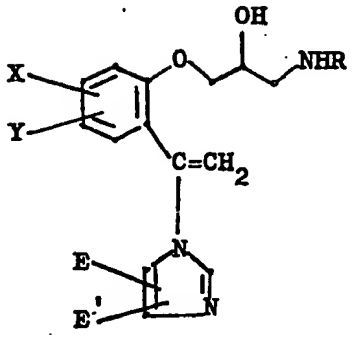
(VIII) (IIIc)

(wherein

W' is a reactive group such as halogen or an ester moiety (e.g. tosyloxy); and A, X, Y and Z have the same significance as given earlier).

Thus the reaction of Compound VIII with Compound IX is performed in an appropriate solvent (e.g. dimethylformamide, benzene, chloroform, tetrahydrofuran, diglyme, dimethylsulfoxide) in the presence of a base such as triethylamine, pyridine, sodium amide, sodium ethoxide, or sodium hydride at between room temperature and the boiling point of the solvent used. For example, o-(1-imidazolyl)-methylphenol is disclosed in Japanese Unexamined Patent Publication No. 164677/1980.

Among the compounds of general formula I a group of compounds with tne general formula Ia is preferred:



(wherein

E and E' are independently hydrogen, C_1-C_2 alkyl or C_2-C_3 alkoxycarbonyl;

R is C_3-C_4 alkyl; and

X and Y are independently hydrogen, methyl, methoxy or chlorine).

The compounds of general formula I and their pharmaceutically acceptable acid addition salts show excellent antiarrhythmic activity. Results of the pharmacological tests are shown below:

1. Test Method:

a) Antiarrhythmic activity (cardiomuscular action to the maximal stimulus frequency):

A certain number of atrium dextrum specimens were made by extracting the heart from male and female guinea-pigs weighing on average 350 to 600 g, and then suspended and fixed in a glass vessel filled with Krebs-Ringer-sodium carbonate solution (30°C) in which a mixture of 95 % oxygen and 5 % carbon dioxide was continuously introduced. The automatism of the specimens was recorded on the oscillograph. Maximal stimulus frequency was confirmed by affording a stimulus of the atrium dextrum from the exciting electrode equipped to a retainer.

After previously treating with a test compound for 10 minutes, the percent reduction (%) in the maximal stimulus frequency was calculated by observing the reduction in the maximal frequency [Dawes, G.S.: Brit. J. Pharmacl., 1, 90 (1946)].

b) Acute toxicity:

The lethal dose was determined by administering a test compound in the form of a physiological brine solution into the tail venae of SLC-DDY male mice weighing from

25 to 35 g and alculating the value f LD_{50} by th up and down method [Brownlee, K.A. et al.: J. Am. Stat. As., 48, 262 (1953)].

2. Result:

Table 1 shows the result of the tests. The Test Compound No. corresponds to the number of the example in which the compound is prepared.

Table 1.

Test Compound No.	Reduction in Maximal Stimulus Frequency, %	Acute toxicity, mg/kg
7	38.1	19.8
13	34.5	15.5
17	31.7	36.4
22	35.8	26.5
24	36.1	36.4
25	39.2	22.3
26	35.8	33.9
29	29.0	30.0
30	50.6	28.5
31	42.8	36.4
Quinidine	22.8	53.6

As clearly shown by the above test results, the compounds of general formula I which are the subject of the present invention show excellent antiarrhythmic activity and are useful for treating arrhythmia or for prophylaxis of angina pectoris. Further, the compounds of general formula I are available for treating thrombosis or the like diseases.

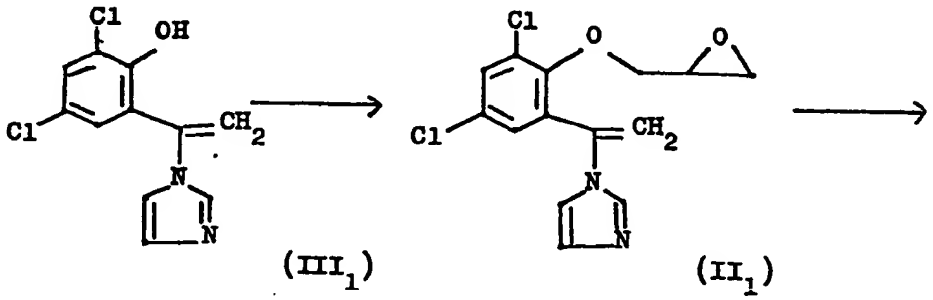
showing platelet aggregati n inhibitory activity.

The compounds of general formula I may be administered enterally or parenterally and formulated in combination with appropriate carriers, diluents, and/or excipients. Customary formulations such as powders, granules, tablets, or capsules for oral administration may be prepared in combination with pharmaceutically acceptable diluents, carriers and/or excipients such as lactose, sucrose, starch, cellulose, talc, magnesium stearate, magnesium oxide, calcium sulfate, gum arabic, gelatin, sodium arginate, sodium benzoate or stearic acid. Injections may be prepared in combination with distilled water, physiological brine or Ringer solution. Appropriate dosage of Compound I to human adults is daily about 5 to about 500 mg per os and about 20 to about 400 mg at one time for intravenous administration.

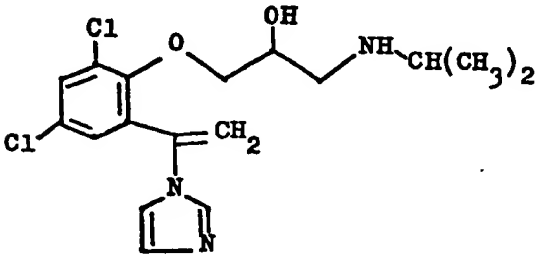
Preferred and practical embodiments of the present invention are illustratively shown in the following examples.

Example 1

1-{2,4-Dichloro-6-[1-(1-imidazolyl)vinyl]-phenoxy}-3-isopropylamino-2-propanol



(III_1) (II_1)



(I_1)

2,4-Dichloro-6-[1-(1-imidazolyl)vinyl]phenol (III_1) (3.9 g) is dissolved in dry dimethylformamide (47 ml), to which 5% sodium hydride (1.10 g) is added and then a solution of epibromohydrin (3.14 g) in dry dimethylformamide (2 ml) is added dropwise. The solution is stirred at 60°C for 1.5 hours, then poured into water and extracted with benzene. The extract is washed with water, dried over sodium sulfate and evaporated to remove the benzene. Oily residue (II_1) is mixed with isopropylamine (20 ml), stirred at 50°C for 19 hours and evaporated

to remove the isopropylamine. To the residue is added water and sodium hydrogencarbonate and then the mixture is extracted with methylene chloride. The extract is washed with water, dried over sodium sulfate and evaporated to remove the solvent. The residue is chromatographed on alumina (Activity II). The fractions eluted with 2-3 % methanol-methylene chloride are collected and evaporated to remove the solvent. The residue is washed with ether-isopropyl ether and filtered to give the title compound (2.1 g) as colorless prisms, mp, 88-90°C. Recrystallization from ethyl acetate-isopropyl ether gives colorless prisms (1.78 g), mp, 88.5-90°C.

Anal. Calcd. for $C_{17}H_{21}O_2N_3Cl_2$:

Calcd. : C, 55.14; H, 5.72; N, 11.35; Cl, 19.15

Found : C, 55.31; H, 5.67; N, 11.33; Cl, 18.89

Examples 2-48

Following the same procedure as in Example 1 the compounds of general formula I listed in Table 2 are obtained.

The abbreviations shown below have the following meanings.

Im = 1-imidazolyl

Py = 1-pyrazolyl

Bim = 1-benzimidazolyl

Tri = 1-(1,2,4-triazolyl)

Pyd = 1-(4-oxo-1,4-dihydropyridyl)

Me = methyl

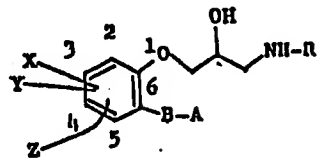
Et = ethyl

i-Pr = isopropyl

i-Bu = isobutyl

t-Bu = t-butyl

d = decomposition



Example No.	Compound I						Mp. (°C)	Molecular Formula	Elemental Analysis			
	A	B	R	X	Y	Z			C	H	N	Cl
2	Im	$C(=CH_2)$	t-Bu	H	H	H	Oil	$C_{18}H_{25}O_2N_3$	68.54 68.31	7.99 8.22	13.32 12.85	- -
3	Im	"	i-Pr	H	H	H	"	$C_{17}H_{23}O_2N_3 \cdot H_2O$	64.66 64.73	7.85 7.73	13.31 12.95	- -
4	Im	"	i-Pr	3-Cl	H	H	79-84	$C_{17}H_{22}O_2N_3Cl \cdot H_2O$	57.70 58.05	6.84 6.79	11.88 11.72	10.02 10.27
5	Im	"	t-Bu	2-Cl	4-Cl	H	135-136.5	$C_{18}H_{23}O_2N_3Cl$	56.26 56.26	6.03 6.03	10.93 10.91	18.45 18.38
6	Im	"	i-Pr	4-Cl	H	H	66.5-67.5	$C_{17}H_{22}O_2N_3Cl$	60.80 60.85	6.60 6.65	12.51 12.39	10.56 10.59
7	Im	"	i-Pr	2-Cl	5-Cl	H	117-122	$C_{17}H_{21}O_2N_3Cl_2$	55.14 54.91	5.72 5.51	11.35 11.17	19.15 19.13
8	Im	CH_2	i-Pr	H	H	H	147.5(d)	$C_{18}H_{25}O_6N_3 \cdot 1/2\ H_2O$	50.20 50.21	5.90 6.03	8.78 8.83	- -

Example No.	Compound I						Mp (°C)	Molecular Formula	Elemental Analysis			
	A	B	R	X	Y	Z			C	H	N	Cl
9	Im	C=CH$_2$	Me	3-Cl	H	H	Oil	$C_{15}H_{18}O_2N_3$ · 1/6 CH_2Cl_2	56.58 56.05	5.74 5.62	13.05 12.55	14.68 15.20
10	Im	C=C(Me)$_2$	i-Pr	4-Cl	H	H	85-87	$C_{19}H_{26}O_2N_3Cl$	62.71 62.70	7.20 7.33	11.55 11.31	9.74 9.75
11	Im	C=CHMe	i-Pr	H	H	H	Oil	$C_{18}H_{25}O_2N_3$ · 1/3 H_2O	67.77 68.09	8.03 8.12	13.17 12.69	- -
12	Im	"	t-Bu	H	H	H	"	$C_{19}H_{27}O_2N_3$ · 1/5 H_2O	68.53 68.88	8.29 8.45	12.62 12.21	- -
13	Im	C=CH$_2$	t-Bu	2-Cl	5-Cl	H	104-105.5	$C_{18}H_{23}O_2N_3Cl_2$	56.26 56.44	6.03 5.98	10.93 10.92	18.45 18.44
14	Im	"	t-Bu	2-Cl	5-Cl	H	147.5-149.5	$C_{18}H_{23}O_2N_3Cl_2$	56.26 56.27	6.03 6.03	10.93 10.62	18.45 18.29
15	Py	"	i-Pr	H	H	H	66.5-67.5	$C_{17}H_{23}O_2N_3$	67.75 67.78	7.69 7.92	13.94 14.03	- -
16	Py	"	i-Pr	4-Cl	H	H	131-132	$C_{17}H_{22}O_2N_3Cl$ · $(COOH)_2$	53.59 53.33	5.68 5.83	9.87 9.81	8.32 8.43

Example No.	Compound I						Mp (°C)	Molecular Formula	Elemental Analysis			
	A	B	R	X	Y	Z			C	H	N	Cl
17	4-EtOCO-5-Me-Im	C=CH_2	i-Pr	H	H	H	Oil	$C_{21}H_{29}O_4N_3 \cdot 3/5\ H_2O$	63.33 63.65	7.64 7.72	10.55 10.18	- -
18	Im	"	i-Pr	2-Cl	H	H	64-66	$C_{17}H_{22}O_2N_3Cl$	60.80 60.86	6.60 6.67	12.51 12.44	10.56 10.47
19	2-Et-5-Me-Im	"	i-Pr	H	H	H	86.5-87	$C_{20}H_{28}O_2N_3$	69.94 69.93	8.51 8.65	12.24 12.17	- -
20	2-Me-Im	"	i-Pr	H	H	H	65-66	$C_{18}H_{25}O_2N_3 \cdot 3/5\ H_2O$	66.27 66.23	8.10 7.99	12.88 12.85	- -
21	Bim	"	i-Pr	H	H	H	148-149(d)	$C_{21}H_{25}O_2N_3 \cdot (COOH)_2 \cdot 1/2\ H_2O$	61.32 61.85	6.26 6.64	9.33 9.03	- -
22	Bim	"	t-Bu	H	H	H	105-106	$C_{22}H_{27}O_2N_3$	72.30 72.40	7.45 7.39	11.50 11.26	- -
23	2-Me-Im	"	t-Bu	H	H	H	70-71	$C_{19}H_{27}O_2N_3$	69.27 69.14	8.26 8.46	12.76 12.66	- -
24	4-Me-Im	"	i-Pr	H	H	H	Oil ※	$C_{18}H_{25}O_2N_3$	68.54 68.21	7.99 8.19	13.32 12.65	- -
25	Py	"	t-Bu	H	H	H	75-76	$C_{18}H_{25}O_2N_3$	68.54 68.43	7.99 8.11	13.32 13.40	- -

Example No.	Compound I						Mp (°C)	Molecular Formula	Elemental Analysis			
	A	B	R	X	Y	Z			C	H	N	Cl
26	Im	C=CH_2	i-Pr	2-Cl	3-Cl	H	124(d)	$C_{17}H_{21}O_2N_3Cl_2$· 2$(COOH)_2$·1/2 H_2O	45.09 45.11	4.68 4.57	7.51 7.29	12.68 12.33
27	Im	"	i-Pr	3-Cl	5-Cl	H	Oil	$C_{17}H_{21}O_2N_3Cl_2$	55.14 54.83	5.70 5.73	11.35 10.75	19.15 18.96
28	Im	"	i-Pr	3-Cl	4-Cl	H	"	$C_{17}H_{21}O_2N_3Cl_2$· 1/5 H_2O	54.61 54.43	5.77 5.83	11.23 10.96	18.97 19.01
29	Im	"	i-Pr	2-OMe	H	H	"	$C_{18}H_{25}O_2N_3$· H_2O	64.84 64.75	8.16 7.92	12.60 12.02	- -
30	Im	"	i-Pr	2-Cl	5-Me	H	126(d)	$C_{18}H_{24}O_2N_3Cl$ ·5/3$(COOH)_2$	51.26 50.77	5.51 5.61	8.40 8.24	7.09 7.15
31	Tri	"	i-Pr	H	H	H	156-157	$C_{16}H_{22}O_2N_4$· $(COOH)_2$	55.09 54.78	6.17 6.19	14.28 14.17	- -
32	Py	CH_2	t-Bu	H	H	H	177-177.5(d)	$C_{17}H_{25}O_2N_3$· $(COOH)_2$·1/10 H_2O	57.74 57.36	6.94 7.02	10.63 10.63	- -
33	Py	"	i-Pr	H	H	H	64-65	$C_{16}H_{23}O_2N_3$	66.41 66.30	8.01 8.18	14.52 14.63	- -
34	Py	C=CH_2	t-Bu	4-Cl	H	H	107-109(d)	$C_{18}H_{24}O_2N_3Cl$· $(COOH)_2$	54.61 54.55	5.96 5.98	9.55 9.37	8.06 8.04

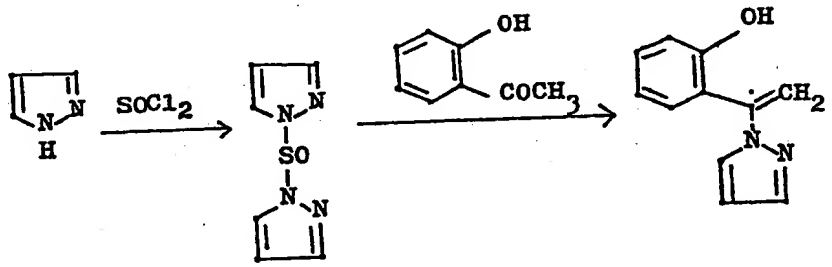
Example No.	Compound I						Mp (°C)	Molecular Formula	Elemental Analysis			
	A	B	R	X	Y	Z			C	H	N	Cl
35	Bim	$C\equiv CH_2$	i-Pr	2-OMe	H	H	147-148(d)	$C_{22}H_{27}O_3N_3 \cdot (COOH)_2 \cdot 1/5H_2O$	60.67 60.51	6.24 6.08	8.85 8.81	- -
36	Bim	"	t-Bu	2-OMe	H	H	110-111	$C_{23}H_{29}O_3N_3$	69.85 69.67	7.39 7.30	10.63 10.55	- -
37	Im	"	t-Bu	2-Cl	5-Me	H	131-132	$C_{19}H_{26}O_2N_3Cl$	62.71 62.64	7.20 7.15	11.55 11.46	9.74 9.88
38	Im	"	t-Bu	2-Me	H	H	145(d)	$C_{19}H_{27}O_2N_3 \cdot (COOH)_2 \cdot 5H_2O \cdot 1/5\ CH_3CN$	57.67 57.96	7.15 6.76	10.06 10.22	- -
39	Im	"	t-Bu	2-Me	4-Cl	H	76-78(d)	$C_{19}H_{26}O_2N_3Cl \cdot 2(COOH)_2$	50.79 50.84	5.56 5.82	7.73 7.51	6.52 6.78
40	Im	"	i-Pr	2-Me	4-Cl	H	123-127(d)	$C_{18}H_{24}O_2N_3Cl \cdot 2(COOH)_2 \cdot 1/2H_2O$	49.03 48.78	5.42 5.18	7.80 7.51	6.58 6.48
41	Im	"	i-Pr	2-Cl	4-Me	5-Me	99-100.5	$C_{19}H_{26}O_2N_3Cl$	62.71 62.80	7.20 7.31	11.55 11.44	9.74 9.85
42	Im	"	t-Bu	2-Cl	4-Me	5-Me	129-130	$C_{20}H_{28}O_2N_3Cl$	63.57 63.51	7.47 7.51	11.12 10.91	9.38 9.44

Example No.	Compound I						Mp (°C)	Molecular Formula	Elemental Analysis			
	A	B	R	X	Y	Z			C	H	N	Cl
43	Im	$CH=CH_2$	t-Bu	2-Me	5-Me	H	136.5-140	$C_{20}H_{29}O_2N_3$	69.94 70.01	8.51 8.64	12.24 12.21	- -
44	Im	"	i-Pr	2-Me	5-Me	H	109-110	$C_{19}H_{27}O_2N_3$	69.27 69.06	8.26 8.44	12.76 12.62	- -
45	Im	"	t-Bu	2-Me	4-Me	H	111-112	$C_{20}H_{29}O_2N_3$	69.94 69.61	8.51 8.64	12.24 12.02	- -
46	Im	"	i-Pr	2-Me	4-Me	H	86-87.	$C_{19}H_{27}O_2N_3$	69.27 69.18	8.26 8.48	12.76 12.68	- -
47	Pyd	"	i-Pr	H	H	H	173.5-174.5 (d)	$C_{19}H_{24}O_3N_2 \cdot 3/2(COOH)_2$	57.01 56.95	5.87 5.89	6.04 5.97	- -

※ $2(COOH)_2 \cdot 1/2CH_3ON$ salt mp. 59-63 °C (d)

Reference 1

Preparation of 2-[1-(1-pyrazolyl)vinyl]phenol



Pyrazole (9 g) is suspended in methylene chloride (45 ml), to which thionyl chloride (3.93 g) is added dropwise at 0°C with stirring. o-Hydroxyacetophenone (3 g) is also added thereto after 10 minutes. The mixture is stirred at room temperature for 4 hours, then ice water is added thereto, and extracted with methylene chloride after neutralized with an aqueous solution of sodium hydrogencarbonate. The extract is washed with water, dried over sodium sulfate and evaporated to remove the solvent. The residue is chromatographed on silica gel and eluted with 1-2% methanol-methylene chloride to give the title compound (198 mg). Recrystallization from ethyl acetate-petroluem ether gives crystals melting at 107.5-109°C.

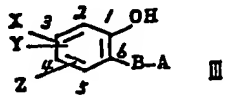
Anal. Calcd. for $C_{11}H_{10}ON_2$

Calcd. : C, 70.95; H, 5.41; N, 15.05

Found : C, 71.25; H, 5;34; N, 15.24

Th above compound is us d as starting compound in Examples 15 and 25.

Starting compounds in other examples are prepared in the same manner. The melting points of the new starting compounds of general formula III are shown as follows:

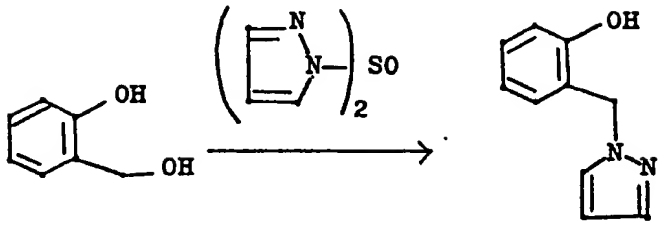


III

Related Example	Compound III					Mp (°C)
	A	B	X	Y	Z	
1,5	Im	$CH=CH_2$	2-Cl	4-Cl	H	216-217
4,9	Im	"	3-Cl	H	H	175-178
6	Im	"	4-Cl	H	H	182-183
7,13,14	Im	"	2-Cl	5-Cl	H	182-184
10	Im	$CH=C(Me)_2$	4-Cl	H	H	190-194
11,12	Im	CH=CHMe	H	H	H	182-186.5
16,34	Py	$CH=CH_2$	4-Cl	H	H	140-142.5
17	4-EtOCO-5-Me-Im	"	H	H	H	216-218
18	Im	$CH=CH_2$	2-Cl	H	H	149-151.5
19	2-Et-5-Me-Im	"	H	H	H	212-213
20,23	2-Me-Im	"	H	H	H	170-172
24	4-Me-Im	"	H	H	H	165-170
26	Im	"	2-Cl	3-Cl	H	207-209
27	Im	"	3-Cl	5-Cl	H	193-194
28	Im	"	3-Cl	4-Cl	H	252-253.5
29	Im	"	2-OMe	H	H	153-154
30,37	Im	"	2-Cl	5-Me	H	152.5-153.5
31	Tri	"	H	H	H	153-156
35,36	Bim	"	2-OMe	H	H	192-193(d)
38	Im	"	2-Me	H	H	141-143
39,40	Im	"	2-Me	4-Cl	H	160-161.5
41,42	Im	"	2-Cl	4-Me	5-Me	152-153
43,44	Im	"	2-Me	5-Me	H	130-131
45,46	Im	"	2-Me	4-Me	H	134-135

Reference 2

o-(1-Pyrazolylm thyl)phenol



Pyrazole (24.68 g) is mixed with dry methylene chloride (123 ml), to which thionyl chloride (10.78 g) is added with stirring under ice cooling. The mixture is stirred for 10 minutes and o-hydroxybenzyl alcohol (7.5 g) is added thereto. The mixture is stirred at room temperature for 1.5 hours, then neutralized with an aqueous solution of sodium hydrogencarbonate and extracted with methylene chloride. The extract is washed with water, dried and evaporated to remove the solvent. The residue is chromatographed on silica gel. Eluates with benzene-methylene chloride are collected, evaporated to remove the solvent, washed with ethyl acetate-isopropyl ether, and filtered to give the title compound (5.95 g), mp. 123-124°C.

Anac. Calcd. for $C_{10}H_{10}ON_2$:

Calcd. : C, 68.95; H, 5.79; N, 16.08

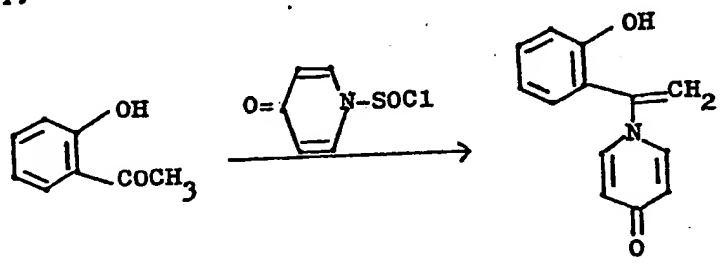
Found: : C, 69.23; H, 5.74; N, 16.11

The above compound is used as starting compound

in Examples 32 and 33.

Reference 3

Preparation of 1-[1-(2-hydroxyphenyl)vinyl]-4-pyridone



4-Hydroxypyridine (838 mg) is mixed with a mixture of triethylamine (890 mg) and dry methylene chloride (8.4 ml) and stirred under cooling. A solution of thionyl chloride (1.048 g) in methylene chloride (3 ml) is added dropwise thereto at the temperature kept at about 10°C and then the mixture is stirred for further 30 minutes and added dropwise to a mixture of o-hydroxyacetophenone (1 g), triethylamine(890 mg) and dry methylene chloride (10 ml) at the same temperature with stirring. The resultant mixture is stirred at room temperature for 15.5 hours and then ice water is added thereto. The mixture is made alkaline with sodium hydrogencarbonate and extracted with methylene chloride. The extract is washed with water, dried and evaporated to remove the solvent. The residue is chromatographed on silica gel. Eluates

with 7% methanol-methylene chlorid are collected and evaporated to remove the solvent. The yielded crystals are recrystallized from methanol-ethyl acetate to give the title compound (436 mg), mp. 201-203°C.

Anal. Calcd. for $C_{13}H_{11}O_2N$:

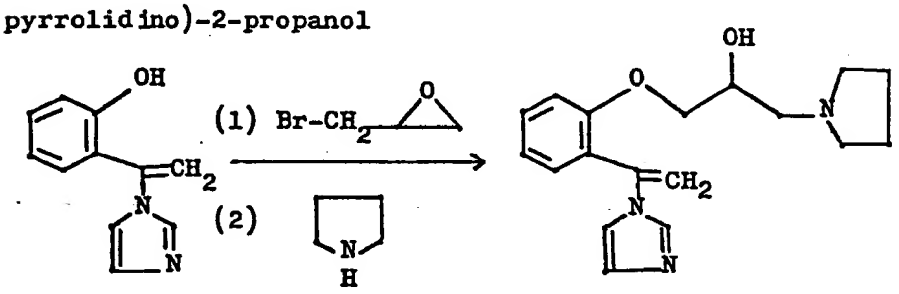
Calcd. : C, 73.22; H, 5.20; N, 6.57

Found : C, 73.17; H, 5.09; N, 6.54

The above compound is used as starting compound in Example 47.

Example 48

1-{2-[1-(1-imidazolyl)vinyl]phenoxy}-3-(1-pyrrolidino)-2-propanol



A mixture of 2-[1-(1-imidazolyl)vinyl]phenol (4 g), 50% sodium hydroxide (1.55 g), dimethyl formamide (20 ml) and epibromohydrin (4.41 g) is heated at 50°C for 1 hour with stirring. The reaction mixture is treated in the same manner as in Example 1. The resultant epoxide is kept at room tempetature for 20 hours after addition of pyrrolidine (6 ml) and then evaporated to remove the pyrrolidine. The residue is mixed with benzene

and evaporated to remove the solvent. The residue is chromatographed on alumina. The eluates with 2% methanol-methylene chloride are collected and evaporated to remove the solvent. The residue is recrystallized from ethyl acetate-isopropyl ether to give the title compound (720 mg), mp. 74-76°C.

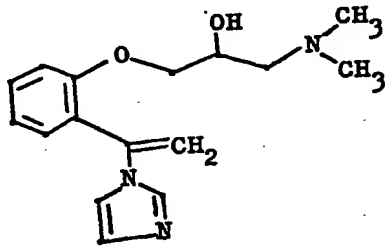
Anal. Calcd. for $C_{18}H_{23}O_2N_3$:

Calcd. : C, 68.94; H, 7.40; N, 13.41

Found : C, 69.00; H, 7.44; N, 13.37

Example 49

1-{2-[1-(1-imidazolyl)vinyl]phenoxy}-3-dimethylamino-2-propanol



The same procedure as in Example 48 gives the title compound, mp. 62.5-63.5°C.

Anal. Calcd. for $C_{16}H_{21}O_2N_3$:

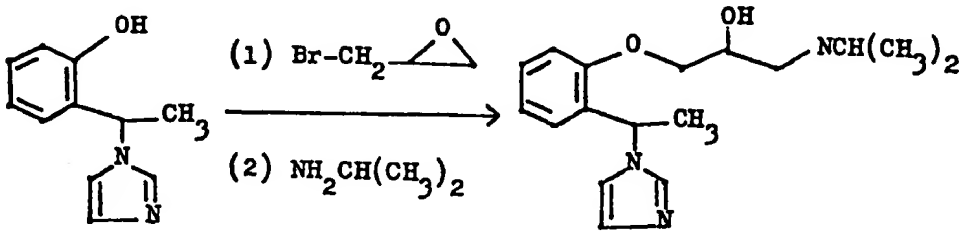
Calcd. : C, 66.87; H, 7.37; N, 14.62

Found : C, 66.73; H, 7.33; N, 14.66

Example 50

1-{2-[1-(1-imidazolyl)ethyl]phenoxy}-3-isopropyl-

amino-2-propanol



The same procedure as in Example 1 is practised with 6-[1-(1-imidazolyl)ethyl]phenol (1.0 g), 50% sodium hydride (385 mg), dehydrated dimethylformamide (10 ml) and epibromohydrin (1.10 g) to give an epoxide, which is mixed with isopropylamine (8 ml) and refluxed for 1 hour. The reaction mixture is treated in usual manner and the resultant residue is chromatographed on alumina (activity II). The eluates with 1-3% methanol-methylene chloride are collected and evaporated to remove the solvent. The title compound (618 mg) is yielded as an oil.

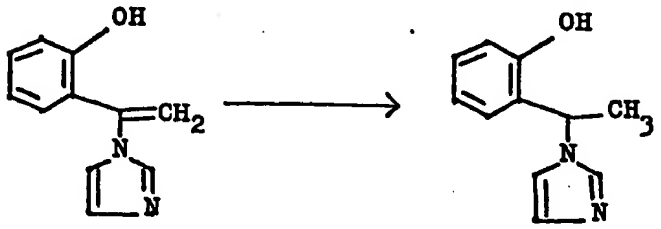
Anal. Calcd. for $C_{17}H_{25}O_2N_3 \cdot 3/5H_2O$

Calcd. : C, 64.98; H, 8.40; N, 13.37

Found : C, 65.22; H, 8.45; N, 12.92

Reference 4

2-[1-(1-imidazolyl)ethyl]phenol



A mixture of 6-[1-(1-imidazolyl)vinyl]phenol (500 mg), methanol (20 ml), 14% hydrochloric acid-methanol (5 ml) and platinum oxide monohydrate (100 mg) is stirred in hydrogen atmosphere and filtered when the hydrogen absorption is finished, about 1.5 hours later. The filtrate is condensed, neutralized with an aqueous solution of sodium hydrogencarbonate and extracted with methylene chloride. The extract is washed with water, dried and evaporated to remove the solvent. The residue is recrystallized from ethyl acetate-isopropyl ether to give the title compound (456 mg), mp. 170.5-172°C.

Anal. Calcd. for $C_{11}H_{12}ON_2$:

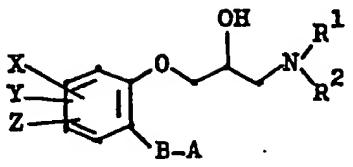
Calcd. : C, 70.18; H, 6.43; N, 14.88

Found : C, 70.25; H, 6.51; N, 14.78

The product is used as starting compound in Example 50.

What is claimed is:

1. A compound of the general formula I:



(I)

(wherein

A is a 5- or 6-membered unsaturated heterocycle containing 1-3 nitrogen atoms or a benzimidazolyl optionally each substituted by 1-3-substituents selected from oxo, C_1-C_4 alkyl, C_1-C_4 alkoxy, C_2-C_6 alkoxycarbonyl and halogen;

B is $>CHR^3$ or $>C=CR^4R^5$

in which R^3, R^4 and R^5 are independently hydrogen or C_1-C_4 alkyl;

R^1 is C_1-C_4 alkyl;

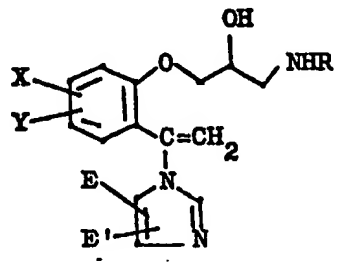
R^2 is hydrogen or C_1-C_4 alkyl; or

R^1-N-R^2 is pyrrolidinyl, piperidino, piperazino or morpholino; and

X, Y and Z are independently hydrogen, C_1-C_4 alkyl, C_1-C_4 alkoxy or halogen)

and pharmaceutically acceptable acid addition salts thereof

2. A compound of the general formula Ia:



(Ia)

(wherein

E and E' are independently hydrogen, C_1-C_2 alkyl or C_2-C_3 alkoxycarbonyl;

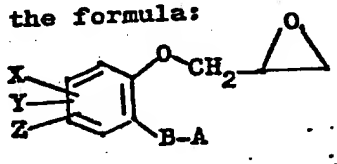
R is C_3-C_4 alkyl; and

X and Y are independently hydrogen, methyl, methoxy or chlorine)

3. A compound according to claim 1, namely 1-{2,5-dichloro-6-[1-(1-imidazolyl)vinyl]phenoxy}-3-isopropylamino-2-propanol.

4. A compound according to claim 1, namely 1-{2,5-dichloro-6-[1-(1-imidazolyl)vinyl]phenoxy}-3-isopropylamino-2-propanol.

5. Process for preparing the compound as claimed in claim 1 which comprises reacting a compound of the formula:



(wherein A, B, X,Y and Z have the same significance as given earlier)

with a compound of the formula:

R^1—NH—R^2

(wherein R^1 and R^2 have the same significance as given earlier)

in the presence or absence of a solvent at a temperature from about 25°C to about 100°C.

6. A pharmaceutical compositi n comprising an effectiv amount f the compound as claimed in claims 1 to 4 and pharmaceutically acceptable diluents, carriers and/or excipients.

7. Use of a compound as claimed in claims 1 to 4 for preparing a pharmaceutical composition useful for treating arrhythmia, for the prophylaxis of angina pectoris or for treating thrombosis.